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10/523,982	03/28/2005	Akira Kakizuka	2005_0199A	1176

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,982	KAKIZUKA ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 7-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment to the claims filed on July 28, 2008, has been received and entered. Claims 4-6 have been canceled. Claims 7-9 are pending in this application.

Election/Restrictions

Applicant's election of claims 1-2 (group I) in the reply filed on June 20, 2006 was acknowledged. Applicants' have also elected cells obtained from established human or non-human cell line; that is adipocyte cells; and BAT as species for examination in the reply filed March 5, 2008. Claims 7-9 are under consideration.

Maintained-Claim Rejections- 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Spiegelman et al (US Patent publication no. 2003/0124598, dated 7/3/2003, effective filing date 11/09/2001, IDS), Vega et al (Mol Cell Biol. 2000 March; 20(5): 1868-1876, art of record)/ Vega et al (Dissertation Abstracts International, (1999) Vol 60, No. 9B, p. 4366) and Saldek et al (Molecular and Cellular Biology, 1997, 5400-5409, art of record).

Spiegelman also discloses a method of screening drug that has an ability to modulate ERRL1 (PGC-1b) binding to a target molecule (a nuclear receptor or HCF) by coupling the ERRL1 (PGC-1b), target molecule with a radioisotope or enzymatic label such that binding of the PGC-1b (ERRL) target molecule to ERRL1 (PGC-1b) could be determined (see para. 193-194 of the specification).

Regarding claim 7, Spiegelman et al teach a cell-based assay comprising contacting a cell expressing an ERRL1 (PGC-1beta) target molecule a nuclear receptor or HCF with a test

compound and determining the ability of the test compound to modulate (stimulate or inhibit) the activity of the nuclear receptor target molecule. It is reported that the ability of the test compound to modulate the activity of target molecule (nuclear receptor) of ERRL1 can be accomplished by determining the ability of the ERRL1 protein to bind to or interact with the target nuclear receptor or by determining the transcriptional activity of the nuclear receptor target molecule (see para. 199). Spiegelman reported that the ability of a test compound to modulate ERRL1 activity can also be measured by contacting a cell (a brown adipose cell) with the test compound and measuring the number of mitochondria or the level of mitochondrial function in the cell as compared to a control cell not contacted with the test compound. The number of mitochondria can be measured by analyzing the amount of mitochondrial DNA present in the cell by Southern blotting (see para. 196). Spiegelman et al teach PGC-1beta induces mitochondrial gene expression MCAD and CPT-1 (see figure 10). It is noted that that PGC-1 homologue named PGC-1β is structurally similar to ERRL1 as stated in previous office action (see page 26 lines 11-22 of the specification) and meets the limitation of ERRL1. Furthermore, Spiegelman et al also disclose screening assay in cells of mammalian origin including brown adipose cell derived from brown adipose tissue such as a HIB1B cell, a heart cell, or a liver cell meeting the limitation of claims 8-9 (see para. 55 and 193). While, Spiegelman teaches contacting cells expressing nuclear receptor or HCF with candidate compound and then measuring the binding of ERRL1 with other nuclear receptor and also reported measuring the activity of MCAD in mammalian tissue cells to identify agent that modulates the binding or interaction of ERRL1 with nuclear receptor or induces the activity of MCAD or other mitochondrial enzymes, but differed from claimed invention by not explicitly teaching the nuclear receptor being ERR.

The deficiency of Spiegelman is cured by Vega who reported the transcriptional induction of nuclear gene encoding a key mitochondrial FAO enzyme (MCAD) gene during brown adipocyte differentiation required the pleiotropic nuclear receptor response element, NREE-1 (see abstract). Additionally, Vega identifies MCAD as potential ERR alpha target (see abstract). Vega et al also show that the co-activator PGC co operates with PPAR alpha in the transcriptional control of nuclear gene encoding mitochondrial fatty acid oxidation enzyme (MCAD) (see figure 2 of Vega MCB paper).Specifically, Vega et al teach over expression of a

nuclear receptor (PPARα) and ERRL1 (PGC-1) alone or together in the 3T3-L1 cell line, using a retroviral expression system. It is disclosed 3T3-L1 cells closely resemble the white adipocyte, a cell with inherent low expression of mitochondrial FAO enzymes. Vega et al teach infecting preadipocytes with recombinant retroviral particles encoding LacZ (control), nuclear receptor (PPARa), PGC-1, or PPARa and PGC-1 in presence or absence of the known activator, ETYA. Vega et al also measure the activity of nuclear receptor for expressing the level of expression PGC-1, and several mitochondrial FAO enzyme genes such as MCAD, LCAD, and CPT I (see figure 2-4, page 1870, col. 3, to col. 2, para. 1). However, Vega differed from claimed invention by not disclosing contacting a test sample of cultured cells with candidate agent, wherein said cell express ERRalpha.

Sladek et al teach ERR alpha is most highly expressed in kidney, heart, and brown adipocytes, tissues which binds to an ERRa response element (ERRE) containing a single consensus half-site, TNAAGGTCA. Sladek et al teach MCAD nuclear receptor response element 1 (NRRE-1) interacts *in vitro* with ERRa expressed in COS-7 cells and supershift assay shows that endogenous ERRalpha present in nuclear extracts obtained from a brown fat tumor cell line (HIB) interacts with NRRE-1 (see figure 7).

Accordingly, in view of the teachings of Spiegelman et al, Vega and Saldek, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the method of screening compound disclosed by Spiegelman et al to substitute target molecule (nuclear receptor or HCF) with functionally equivalent another nuclear receptor ERRα or other isoforms of ERR with a reasonable expectation of success. At the time of the invention, ERRL1 was known to induce MCAD gene during brown adipocyte differentiation that requires the pleiotropic nuclear receptor response element; NREE-1 and PGC-1 to co operate with PPAR alpha in the transcriptional control of MCAD (see Vega). Given that one of ordinary skill in the art was aware that MCAD nuclear receptor response element 1 (NRRE-1) interacts *in vitro* with nuclear receptor ERR alpha. It would have been *prima facie* obvious to one of ordinary skill in the art to pursue the known options with his or her technical grasp to contact a cultured cells with a compound that express nuclear receptor and comparing the activity of several mitochondrial FAO enzyme genes such as MCAD, LCAD with that of control cells

cultured with ERRL1 without the compound with reasonable expectation for the co-activation of ERR alpha by ERRL1 (PGC-1). Spiegelman et al had already sought to screen compounds by a method comprising contacting cells that express ERRL1 (PGC-1) and target nuclear receptor and then measuring the binding of ERRL1 (PGC-1) to the nuclear receptor in order to identify the candidate compound (supra). Furthermore, Vega provided the guidance that forced expression of ERR increases the MCAD activity in the cells (see page 39 and abstract). Therefore, given that orphan nuclear ERR was known to interact with MCAD, while co-activator ERRL1 was also involved in the transcriptional control of MCAD. It would have *prima facie* obvious for one of ordinary skill to modify the method disclosed by Spiegelman to include ERRα as the target molecule with reasonable expectation of achieving predictable result in screening compounds. Furthermore, limitation of claim 7, step 4 would also be obvious as compound increasing the activity for MCAD gene must necessarily have higher level than that of control sample, wherein compound increases activity of ERR for expressing MCAD in view of teaching of Spiegelman and Vega. One who would practiced the invention would have had reasonable expectation of success because molecular cloning of sequences, co transfection was standard technique at the time of filing of this application and Spiegelman et al, Vega and Saldek sought to study the interaction of EERL1 with the nuclear receptor by transcriptional regulation of MCAD.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' cancellation of claims 4-6 renders their rejections moot. To the extent that Applicants' arguments are pertinent to the standing rejection of claim 7-9, they are addressed as follows:

Applicants disagree with the rejection of claim 7-9 over Spiegelman et al, Vega and Saldek, arguing that although relationship between ERRL1, ER and MCAD was known. However, it was not previously confirmed that MCAD gene expression controls energy balance because no *in vivo* substance was known to regulate ERR. Applicants argue that ERRL1 was previously known as PGC-2 that is different from PGC-1 (See page 3 of the argument). Applicants assert that relationship between PGC-1, PPAR and MCAD and not between PGC-2,

ER and MCAD. Applicants also cite Figure 1 to show the differences between PGC-1 and PGC-2. Applicants also assert that cited reference fails to teach in vivo activity of ERRL1 (see page 4). Applicants' arguments have been fully considered, but are not found persuasive (see page 4 of the arguments).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have further engaged in selective reading of the teachings of the cited references to formulate the grounds for not teaching the claimed invention. It should be noted that the claimed screening method requires three steps (1) contacting a test sample of cultured cells expressing ERR with a test agent, (2) contacting control sample of said cell with ERRL1 in absence of drug and measuring the activity of ERRR expressing the MCAD gene in test and control sample. With respect to applicants' argument that no substance was known to regulate ERR, it is noted that Sladek, et al explicitly disclose that ERR1 act as a key transcriptional regulator of the gene encoding medium-chain acyl CoA dehydrogenase (MCAD), a pivotal enzyme in mitochondrial fatty acid .beta.-oxidation suggesting that ERR-mediated gene regulation may play important roles in the control of energy balance in the body by regulating fatty acid beta-oxidation (see the entire article, art of record). It should be noted that Sladek, et al teach ERRa present in nuclear extracts obtained from a brown fat tumor cell line (HIB) interacts with NRRE-1, while transcriptional induction of nuclear gene encoding MCAD gene requires the pleiotropic nuclear receptor response element, NREE-1 (see abstract) as per the teaching of Vega et al. Thus, Spiegelman et al need not teach what is clearly taught by Vega and Sladek. Given that one of ordinary skill in the art was aware that MCAD nuclear receptor response element 1 (NRRE-1) interacts *in vitro* with nuclear receptor ERR alpha. It would have been *prima facie* obvious to one of ordinary skill in the art to combine the teaching to modify the method of Spiegelman et al by contacting a cultured cells with a compound that express nuclear receptor ERR and comparing the activity of several mitochondrial FAO enzyme genes such as MCAD, LCAD with that of control cells cultured with ERRL1 without the compound with reasonable expectation for the co-activation of ERR alpha by ERRL1 (PGC-1).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., *in vivo* activity or PGC-2 sequence, controls energy balance) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). With respect to applicants' argument that ERRL1 was previously known as PGC-2 that is different from PGC-1, it should be noted that claims are not limited to PGC-2 or a sequence thereof. In fact, contrary to applicants' assertions specification teaches:

"[a]s the polynucleotide encoding mouse ERRL1, mouse PGC2 cDNA (ERRL1 cDNA: SEQ ID NO: 1) whose nucleotide sequence has been disclosed in SEQ ID NO: 2 ... can be used. Further, as the polynucleotide encoding human ERRL1, the foregoing human PERC cDNA (GenBank No. NM_133263) can be used. Still further, for example, human PRRC gene exists in chromosome 5q33.1 region, and its genomic sequence is publicly known (GenBank No. NT_029289). Therefore, this invention can be carried out by utilizing a promoter region existing in this genomic gene sequence".

In view of foregoing disclosure the recitation of ERRL1 in base claim broadly embrace mouse PGC-2 and variant thereof such as human homolog of PERC. In the instant case, the isolated nucleic acid molecule disclosed by Spiegelman comprise a nucleotide sequence, which is at least about 99.99% or more identical to the entire length of the nucleotide sequence of PGC-1 (page 2 and 3, paragraph 20) that has over 99% sequence homology with mouse PGC-2. Furthermore, it is also noted that Applicants in a post filing publication related with instant invention have synonymously used the term ERRL1 and PGC-1β (see Kamei et al Proc Natl Acad Sci U S A. 2003; 100(21): 12378-83, art of record, cited without relying for the rejection). Therefore, in absence of specific recitation of mouse PGC2 or sequence thereof, the sequence disclosed by Spiegelman is embraced by the breadth of the claim. Given that orphan nuclear (ERR) was known to interact with MCAD, while co-activator ERRL1 was also involved in the transcriptional control of MCAD. It would have *prima facie* obvious for one of ordinary skill to modify the method of Spiegelman by contacting a cultured cells with a compound that express nuclear receptor and comparing the activity of several mitochondrial FAO enzyme genes such as MCAD, LCAD with that of control cells cultured with ERRL1 without the compound with reasonable expectation for the co-activation of ERR alpha by ERRL1 (PGC-1).

Should the claims be amended to state specific PGC-2 or polynucleotide encoding mouse PGC2 (SEQ ID NO: 2), the above obviousness rejection may be overcome pending further consideration.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kakitsuka et al (JP2002058489, dated 2/26/2002, IDS). It is noted that prior art of Kakitsuka et al teach the sequence of PGC-2 that is structurally similar to one disclosed in the instant specification. Kakitsuka et al would be pertinent if the claims are limited to specific sequence of ERLL1.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

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